**LOMUSTINE- lomustine capsule, gelatin coated**
**NextSource Biotechnology, LLC**

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**Lomustine**
**Capsules**

**WARNINGS**

Lomustine should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

Bone marrow suppression, notably thrombocytopenia and leukopenia, which may contribute to bleeding and overwhelming infections in an already compromised patient, is the most common and severe of the toxic effects of Lomustine (see **WARNINGS** and **ADVERSE REACTIONS**).

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see **ADVERSE REACTIONS**). At the recommended dosage, courses of Lomustine should not be given more frequently than every 6 weeks.

The bone marrow toxicity of Lomustine is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see dosage adjustment table under **DOSAGE AND ADMINISTRATION**).

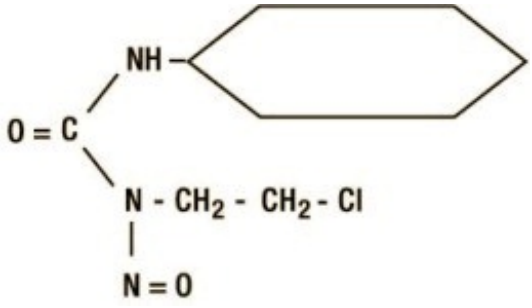
## DESCRIPTION

Lomustine (CCNU) is one of the nitrosoureas used in the treatment of certain neoplastic diseases. It is 1-(2-chloro-ethyl)-3-cyclohexyl-1-nitrosourea. It is a yellow powder with the empirical formula of $C_9H_{16}ClN_3O_2$ and a molecular weight of 233.71. Lomustine is soluble in 10% ethanol (0.05 mg per mL) and in absolute alcohol (70 mg per mL). Lomustine is relatively insoluble in water (<0.05 mg per mL).

It is relatively un-ionized at a physiological pH.

Inactive ingredients in Lomustine Capsules are magnesium stearate and mannitol.

The structural formula is:




Lomustine is available in 10 mg, 40 mg, and 100 mg capsules for oral administration.

## CLINICAL PHARMACOLOGY

Although it is generally agreed that lomustine alkylates DNA and RNA, it is not cross resistant with other alkylators. As with other nitrosoureas, it may also inhibit several key enzymatic processes by

carbamoylation of amino acids in proteins.

Lomustine may be given orally. Following oral administration of radioactive lomustine at doses ranging from 30 $mg/m^2$ to 100 $mg/m^2$, about half of the radioactivity given was excreted in the urine in the form of degradation products within 24 hours.

The serum half-life of the metabolites ranges from 16 hours to 2 days. Tissue levels are comparable to plasma levels at 15 minutes after intravenous administration.

Because of the high lipid solubility and the relative lack of ionization at physiological pH, lomustine crosses the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are 50% or greater than those measured concurrently in plasma.

## INDICATIONS AND USAGE

Lomustine has been shown to be useful as a single agent in addition to other treatment modalities, or in established combination therapy with other approved chemotherapeutic agents in the following:

**Brain tumors**—both primary and metastatic, in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

**Hodgkin's disease**—secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

## CONTRAINDICATIONS

Lomustine should not be given to individuals who have demonstrated a previous hypersensitivity to it.

## WARNINGS

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see ADVERSE REACTIONS). At the recommended dosage, courses of Lomustine should not be given more frequently than every 6 weeks.

The bone marrow toxicity of Lomustine is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see dosage adjustment table under **DOSAGE AND ADMINISTRATION**).

Pulmonary toxicity from Lomustine appears to be dose related (see **ADVERSE REACTIONS**).

Long-term use of nitrosoureas has been reported to be possibly associated with the development of secondary malignancies.

Liver and renal function tests should be monitored periodically (see **ADVERSE REACTIONS**).

### Pregnancy Category D

Lomustine can cause fetal harm when administered to a pregnant woman. Lomustine is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

## PRECAUTIONS

### General

In all instances where the use of Lomustine is considered for chemotherapy, the physician must evaluate

the need and usefulness of the drug against the risks of toxic effects or adverse reactions. Most such adverse reactions are reversible if detected early. When such effects or reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of Lomustine therapy should be carried out with caution and with adequate consideration of the further need for the drug and alertness as to possible recurrence of toxicity.

### Information for Patients

Provide patients with the following information and instructions:

1. In order to provide the proper dose of Lomustine, the dose may be made up of 2 or more different strengths and colors of capsules. Each strength must be dispensed separately by the pharmacist.
2. Lomustine is given as a single oral dose and will not be repeated for at least 6 weeks. Daily use of the recommended dose may lead to toxicities and fatal outcomes.
3. Patients may experience nausea and vomiting that usually last less than 24 hours. Patients may also experience loss of appetite that may last for several days.
4. Instruct patients to contact their physician if they develop any of the following reactions: fever, chills, sore throat, unusual bleeding or bruising, shortness of breath, dry cough, swelling of feet or lower legs, mental confusion, or yellowing of eyes and skin.
5. Instruct patients to wear impervious (rubber or latex) gloves when handling Lomustine Capsules.

### Laboratory Tests

Due to delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose.

Baseline pulmonary function studies should be conducted along with frequent pulmonary function tests during treatment. Patients with a baseline below 70% of the predicted Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity ($DL_{CO}$) are particularly at risk.

Since Lomustine may cause liver dysfunction, it is recommended that liver function tests be monitored periodically.

Renal function tests should also be monitored periodically.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Lomustine is carcinogenic in rats and mice, producing a marked increase in tumor incidence in doses approximating those employed clinically. Nitrosourea therapy does have carcinogenic potential in humans (see **ADVERSE REACTIONS**). Lomustine also affects fertility in male rats at doses somewhat higher than the human dose.

### Pregnancy

### Pregnancy Category D

See **WARNINGS**.

### Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Lomustine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

See **ADVERSE REACTIONS: Pulmonary Toxicity** and **DOSAGE AND ADMINISTRATION**.

### Geriatric Use

No data from clinical studies of Lomustine are available for patients 65 years of age and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Lomustine and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

## ADVERSE REACTIONS

### Hematologic Toxicity

The most frequent and most serious toxicity of Lomustine is delayed myelosuppression. It usually occurs 4 to 6 weeks after drug administration and is dose related. Thrombocytopenia occurs at about 4 weeks postadministration and persists for 1 to 2 weeks. Leukopenia occurs at 5 to 6 weeks after a dose of Lomustine and persists for 1 to 2 weeks. Approximately 65% of patients receiving 130 $mg/m^2$ develop white blood counts below 5000 $wbc/mm^3$. Thirty-six percent developed white blood counts below 3000 $wbc/mm^3$. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.

**Lomustine may produce cumulative myelosuppression, manifested by more depressed indices or longer duration of suppression after repeated doses.**

**The occurrence of acute leukemia and bone marrow dysplasias have been reported in patients following long-term nitrosourea therapy.**

**Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.**

### Pulmonary Toxicity

Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported rarely with Lomustine. Onset of toxicity has occurred after an interval of 6 months or longer from the start of therapy with cumulative doses of Lomustine usually greater than 1100 $mg/m^2$. There is 1 report of pulmonary toxicity at a cumulative dose of only 600 mg.

Delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in patients who received related nitrosoureas in childhood and early adolescence (1–16 years) combined with cranial radiotherapy for intracranial tumors. There appeared to be some late reduction of pulmonary function of all long-term survivors. This form of lung fibrosis may be slowly progressive and has resulted in death in some cases. In this long-term study of carmustine, all those initially treated at less than 5 years of age died of delayed pulmonary fibrosis.

### Gastrointestinal Toxicity

Nausea and vomiting may occur 3 to 6 hours after an oral dose and usually last less than 24 hours. Prior administration of antiemetics is effective in diminishing and sometimes preventing this side effect. Nausea and vomiting can also be reduced if Lomustine is administered to fasting patients.

### Hepatotoxicity

A reversible type of hepatic toxicity, manifested by increased transaminase, alkaline phosphatase, and bilirubin levels, has been reported in a small percentage of patients receiving Lomustine.

### Nephrotoxicity

Renal abnormalities consisting of progressive azotemia, decrease in kidney size, and renal failure have been reported in patients who received large cumulative doses after prolonged therapy with Lomustine. Kidney damage has also been reported occasionally in patients receiving lower total doses.

### Other Toxicities

Stomatitis, alopecia, optic atrophy, and visual disturbances, such as blindness, have been reported infrequently.

Neurological reactions, such as disorientation, lethargy, ataxia, and dysarthria have been noted in some patients receiving Lomustine. However, the relationship to medication in these patients is unclear.

## OVERDOSAGE

Accidental overdose with lomustine has been reported, including fatal cases. Accidental overdose has been associated with bone marrow suppression, abdominal pain, diarrhea, vomiting, anorexia, lethargy, dizziness, abnormal hepatic function, cough, and shortness of breath.

No proven antidotes have been established for Lomustine overdosage. In case of overdose, appropriate supportive measures should be taken.

## DOSAGE AND ADMINISTRATION

The recommended dose of Lomustine in adult and pediatric patients as a single agent in previously untreated patients is 130 mg/m$^2$ as a single oral dose every 6 weeks (see **PRECAUTIONS: Information for Patients** and **HOW SUPPLIED: Directions to the Pharmacist**). In individuals with compromised bone marrow function, the dose should be reduced to 100 mg/m$^2$ every 6 weeks. When Lomustine is used in combination with other myelosuppressive drugs, the doses should be adjusted accordingly. All doses of Lomustine must be rounded to the nearest 10 mg by the prescriber (see **HOW SUPPLIED).**

Doses subsequent to the initial dose should be adjusted according to the hematologic response of the patient to the preceding dose. The following schedule is suggested as a guide to dosage adjustment:

| **Nadir After Prior Dose** | | **Percentage of Prior Dose to be Given** |
|---|---|---|
| **Leukocytes (/mm$^3$)** | **Platelets (/mm$^3$)** | |
| ≥4000 | ≥100,000 | 100% |
| 3000–3999 | 75,000–99,999 | 100% |
| 2000–2999 | 25,000–74,999 | 70% |
| <2000 | <25,000 | 50% |

**A repeat course of Lomustine should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm$^3$; leukocytes above 4000/mm$^3$), and this is usually in 6 weeks. Adequate number of neutrophils should be present on a peripheral blood smear. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.**

## HOW SUPPLIED

Lomustine Capsules are available in individual bottles of 5 capsules each.

| | |
|---|---|
| **NDC** 58181-3032-5 | 100 mg capsules (Green/Green) |
| **NDC** 58181-3031-5 | 40 mg capsules (White/Green) |

**Stability**

Lomustine Capsules are stable for the lot life indicated on package labeling when stored in well-closed containers at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F) [see USP Controlled Room Temperature]. Avoid excessive heat (over 40°C, 104°F).

**Directions to the Pharmacist**

Confirm the total dose prescribed by the physician can be obtained by determining the appropriate combination of capsule strengths. Only the appropriate number of Lomustine capsules required for the administration of a single dose should be dispensed.

In order to provide the proper dose of Lomustine, patients should be aware that the prescribed dose may be made up of 2 or more different strengths and colors of capsules and that each strength must be dispensed separately. Inform patients that Lomustine is taken as a single oral dose and will not be repeated for at least 6 weeks. Daily use of the recommended dose may lead to toxicities and fatal outcomes.

Caution should be exercised when handling Lomustine Capsules. Procedures for proper handling and disposal of anticancer drugs should be utilized. Several guidelines on this subject have been published.[1-4] To minimize the risk of dermal exposure, always wear impervious gloves when handling bottles containing Lomustine Capsules. Lomustine Capsules should not be broken. Personnel should avoid exposure to broken capsules. If contact occurs, wash immediately and thoroughly. More information is available in the references listed below.

**REFERENCES**

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. 2006;63:1172–1193.
4. Polovich M, White JM, Kelleher LO, eds. 2005. Chemotherapy and biotherapy guidelines and recommendations for practice. 2nd ed. Pittsburgh, PA: Oncology Nursing Society.

NEXTSOURCE
Biotechnology

Manufactured by Corden Pharma Latina S.p.A., Sermoneta (LT), Italy for:
NextSource Biotechnolgy, LLC
Miami, FL 33155 USA

To report SUSPECTED ADVERSE REACTIONS, contact NextSource Biotechnology at 855-NSB-2468 (855-672-2468) or FDA at 1-800-FDA-1088 (1-800-332-1088) or www.fda.gov/medwatch.

Rev August 2013

Principal Display Panel - 10 mg Carton Label

**NDC 58181-3030-5 5 capsules**

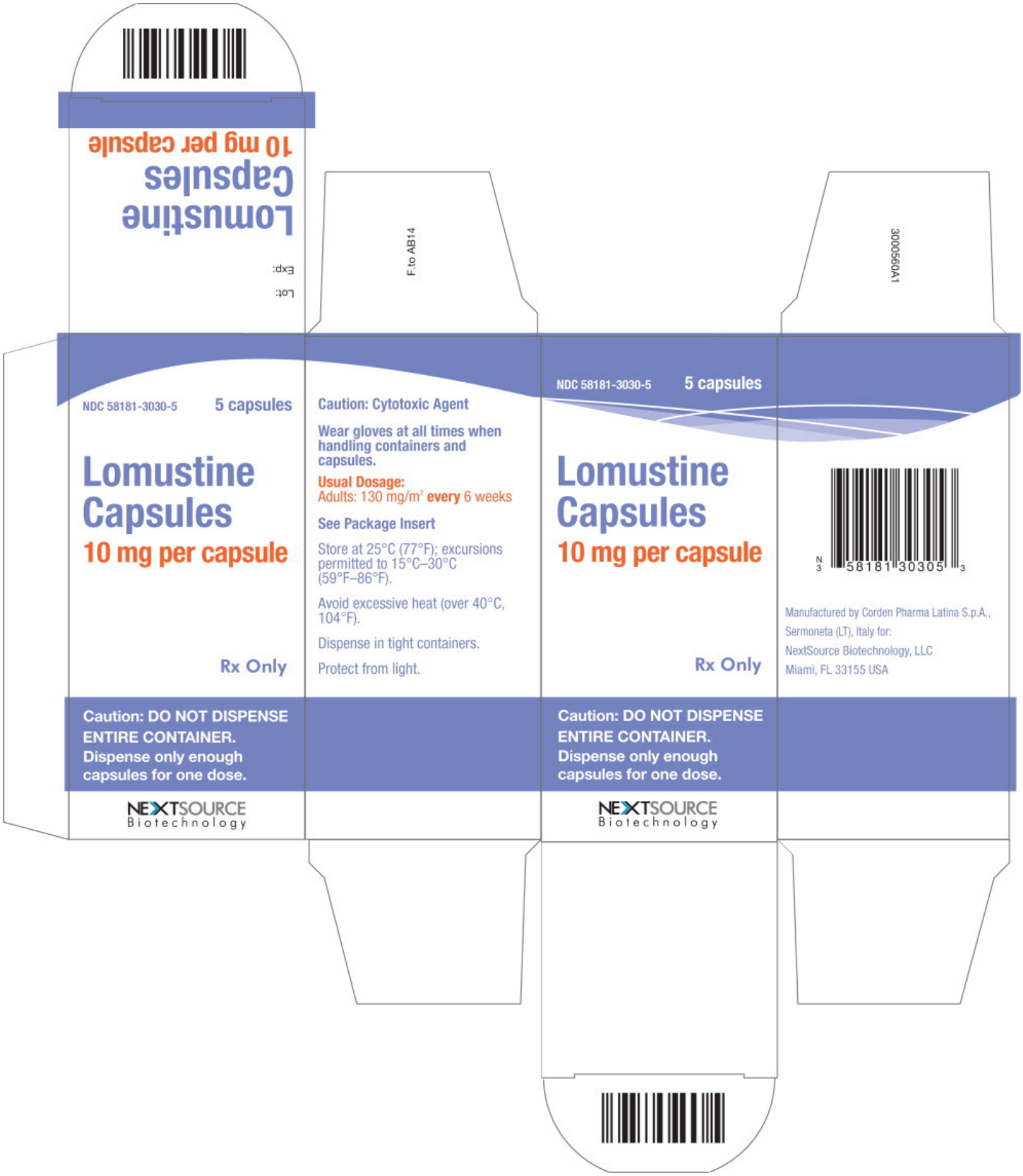
**Lomustine**
**Capsules**
**10 mg per capsule**

**Rx only**

**Caution: DO NOT DISPENSE ENTIRE CONTAINER.**

**Dispense only enough capsules for one dose.**

**NEXTSOURCE**
Biotechnology




Principal Display Panel - 40 mg Carton Label

**NDC 58181-3031-5 5 capsules**

**Lomustine**
**Capsules**
**40 mg per capsule**

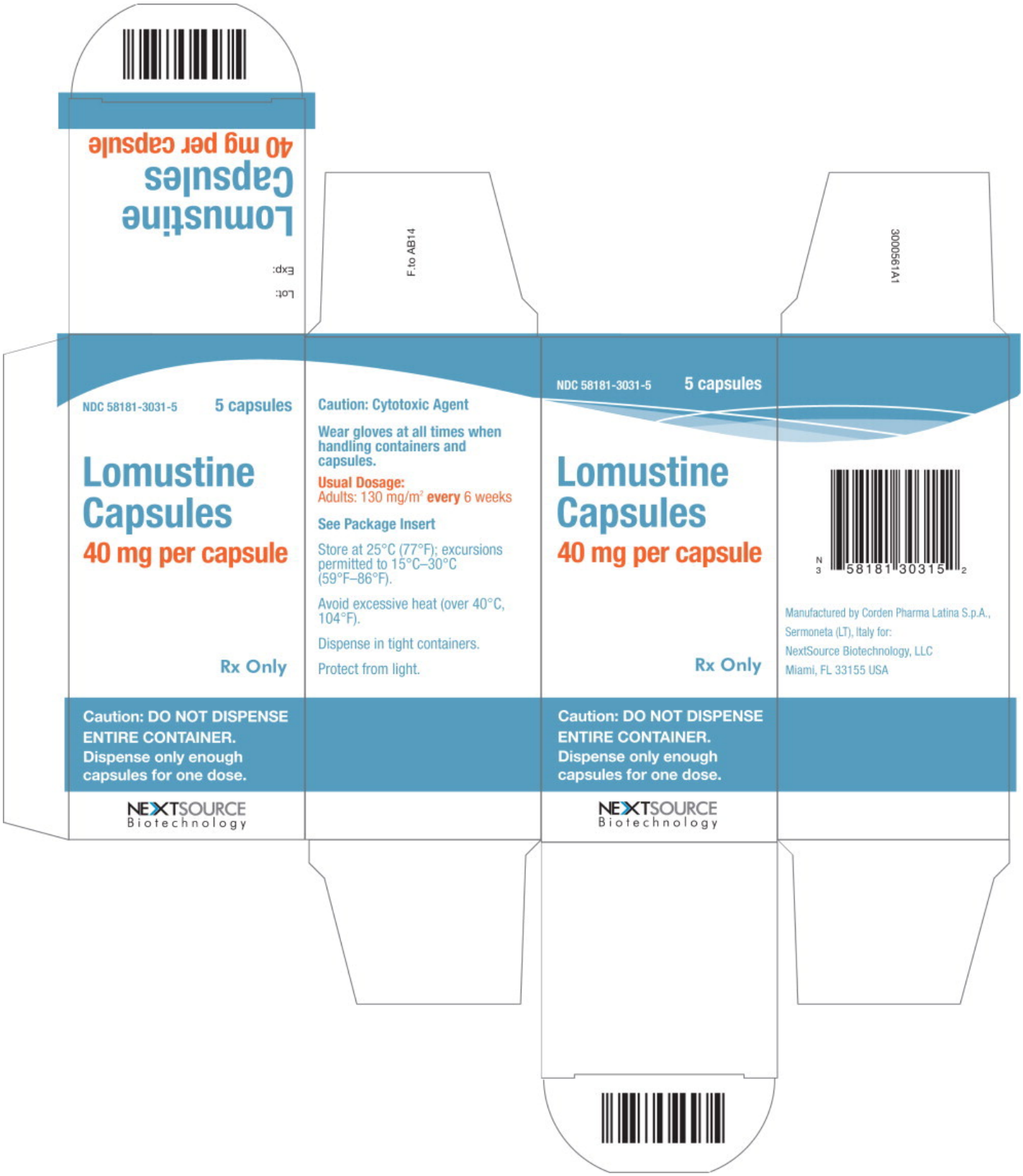
**Rx only**

**Caution: DO NOT DISPENSE ENTIRE CONTAINER.**

**Dispense only enough capsules for one dose.**

**NEXTSOURCE**

Biotechnology



Principal Display Panel - 100 mg Carton Label

**NDC 58181-3032-5 5 capsules**

**Lomustine**
**Capsules**
**100 mg per capsule**

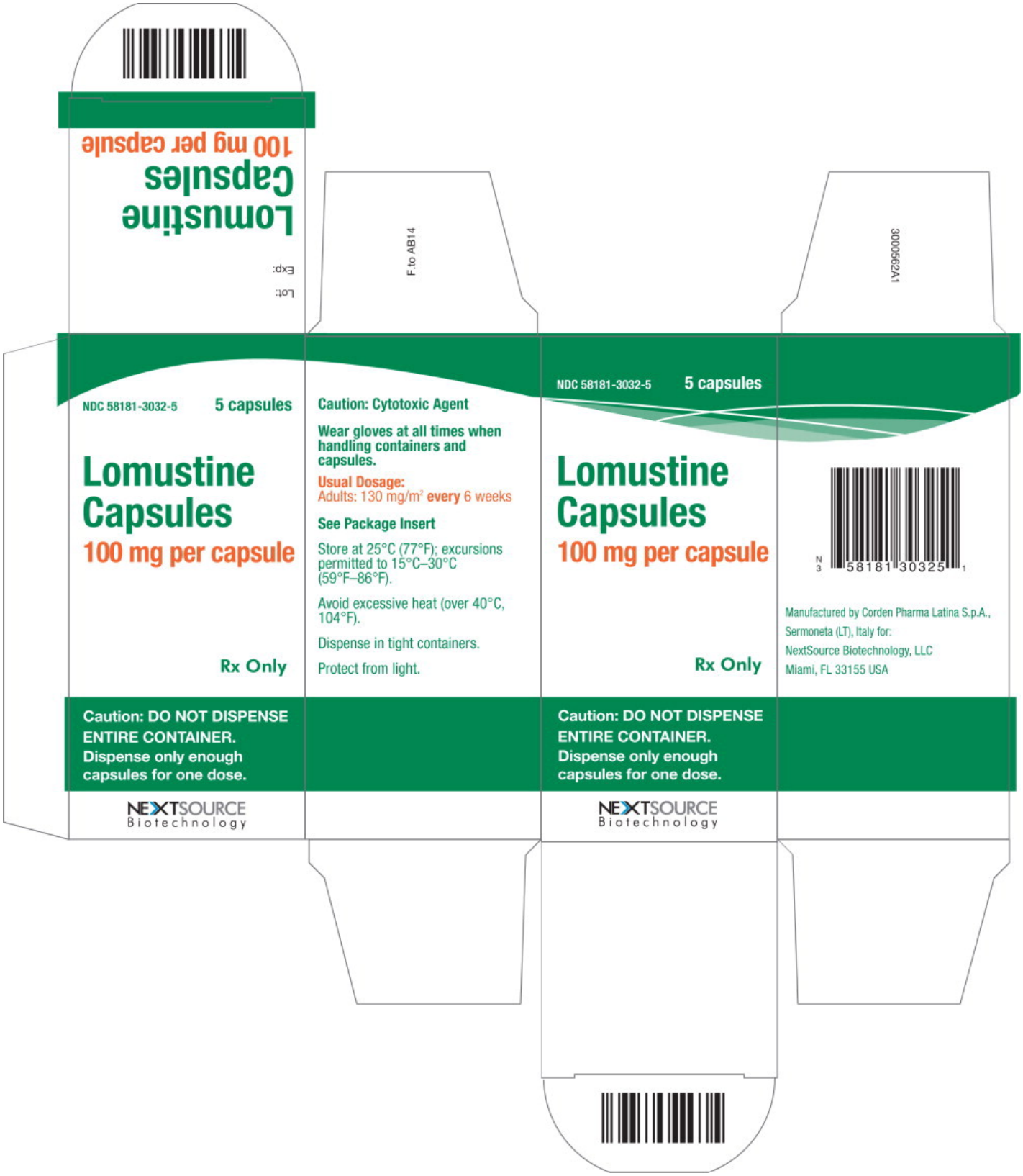
**Rx only**

**Caution: DO NOT DISPENSE**
**ENTIRE CONTAINER.**

**Dispense only enough**
**capsules for one dose.**

**NEXTSOURCE**

Biotechnology




# LOMUSTINE

lomustine capsule, gelatin coated

| Product Information | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG LABEL | **Item Code (Source)** | NDC:58181-3031 |

| | | | |
|---|---|---|---|
| **Route of Administration** | ORAL | **DEA Schedule** | |

### Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|---|---|
| **lomustine** (lomustine) | lomustine | 40 mg |

### Inactive Ingredients

| Ingredient Name | Strength |
|---|---|
| **magnesium stearate** | |
| **mannitol** | |

### Product Characteristics

| | | | |
|---|---|---|---|
| **Color** | green (green) , white (white) | **Score** | no score |
| **Shape** | CAPSULE (CAPSULE) | **Size** | 18mm |
| **Flavor** | | **Imprint Code** | Bristol;3031;40;mg |
| **Contains** | | | |

### Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|---|---|---|---|
| **1** | NDC:58181-3031-5 | 5 in 1 BOTTLE | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| NDA | NDA017588 | 09/27/2013 | |

## LOMUSTINE

lomustine capsule, gelatin coated

### Product Information

| | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG LABEL | **Item Code (Source)** | NDC:58181-3030 |
| **Route of Administration** | ORAL | **DEA Schedule** | |

### Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|---|---|
| **lomustine** (lomustine) | lomustine | 10 mg |

### Inactive Ingredients

| Ingredient Name | Strength |
|---|---|
| **magnesium stearate** | |
| **mannitol** | |

### Product Characteristics

| | | | |
|---|---|---|---|
| **Color** | white (white) | **Score** | no score |
| **Shape** | CAPSULE (CAPSULE) | **Size** | 16mm |
| **Flavor** | | **Imprint Code** | Bristol;3030;10;mg |
| **Contains** | | | |

### Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|---|---|---|---|
| **1** | NDC:58181-3030-5 | 5 in 1 BOTTLE | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| NDA | NDA017588 | 09/27/2013 | |

# LOMUSTINE

lomustine capsule, gelatin coated

### Product Information

| | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG LABEL | **Item Code (Source)** | NDC:58181-3032 |
| **Route of Administration** | ORAL | **DEA Schedule** | |

### Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|---|---|
| **lomustine** (lomustine) | lomustine | 100 mg |

### Inactive Ingredients

| Ingredient Name | Strength |
|---|---|
| **magnesium stearate** | |
| **mannitol** | |

### Product Characteristics

| | | | |
|---|---|---|---|
| **Color** | green (green) | **Score** | no score |
| **Shape** | CAPSULE (CAPSULE) | **Size** | 19mm |
| **Flavor** | | **Imprint Code** | Bristol;3032;100;mg |
| **Contains** | | | |

## Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|---|---|---|---|
| **1** | NDC:58181-3032-5 | 5 in 1 BOTTLE | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| NDA | NDA017588 | 09/27/2013 | |

## Labeler - NextSource Biotechnology, LLC (078779322)

Revised: 8/2013 NextSource Biotechnology, LLC